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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,108	02/01/2006	Takuji Kakigami	868-008	4940

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EXAMINER	
YOUNG, SHAWQUIA	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,108	KAKIGAMI ET AL.	
	Examiner	Art Unit	
	Shawquia Young	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☒ Claim(s) *1-6 and 10-12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/06/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are currently pending in the instant application.

I. *Priority*

The instant application is a 371 of PCT/JP04/00886, filed on January 30, 2004 which claims benefit of Foreign Application JAPAN 2003-023077, filed on January 31, 2003.

II. *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on October 6, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

III. *Restriction/Election*

A. Election: Applicant's Response

Applicants' election with traverse of Group II in the reply filed on March 13, 2007 is acknowledged. The traversal is on the ground(s) that: (1) the variable E in the compound of group II should include the group $-SCH_2-$ and variable A should include the term "optionally substituted".

All of the Applicants' arguments have been considered but have been found partially persuasive. It is pointed out that the restriction requirement is made under 35 U.S.C. 121. 35 U.S.C. 121 gives the Commissioner (Director) the authority to restrict applications to several claimed inventions when those inventions are found to be

independent and distinct. The Examiner has indicated that more than one independent and distinct invention is claimed in this application and has restricted the claimed subject matter accordingly.

Applicants argue that the Group II drawn to a compound of formula (I) that was stated in the Restriction Requirement should include variable E is $-(CH_2)_2-$ or $-SCH_2-$ and component A represents an optionally substituted 6-5 bicyclic heterocyclic group containing nitrogen in the 5-membered ring of the bicyclic heterocyclic group. The Examiner agrees with the Applicant and included in the elected invention the above limitations, however the term "optionally substituted" excludes any heteroaryl or heterocyclic group.

The Restriction Requirement detailed the reasons for restriction between the groups. Different search considerations are involved (i.e., class/subclass searches, databases searches, etc.) for each of the groups listed. The inventions are classified into classes 544, 546 and 548. However, each Class 544, 546 and 548 encompasses numerous patents and published applications. For instance, Class 548 contained 56,976 patents and published applications and Class 546 contained 58,985 patents and published applications. Therefore it would constitute a burden on the Examiner and the Patent Office's resources to examine the instant application in its entirety.

Subject matter not encompassed by elected Group II are withdrawn from further consideration pursuant to 37 CFR 1.142 (b), as being drawn to nonelected inventions.

IV. Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of claims 7-9 is an inhibitor of dipeptidyl peptidase IV activity, comprising the compound of claim 2 as an active ingredient.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art

would recognize that in regards to therapeutic effects of any condition mediated by CB2 receptor activity, whether or not the condition is effected by the activity at CB2 receptors would make a difference.

Applicants are claiming an inhibitor of dipeptidyl peptidase IV activity, comprising the compound of claim 2 as an active ingredient. In the specification on page 22, Applicants state that the claimed compound is useful for prevention and treatment of diseases curable by an inhibitory action on DPP-IV, such as diabetes, its related complications, obesity, autoimmune diseases, etc.

Applicants' claims are therefore are drawn to an inhibitor of dipeptidyl peptidase IV activity that is useful in the treatment and prevention of systemic lupus erythematosus, an autoimmune disease.

Lupus erythematosus is a chronic autoimmune disease that is potentially debilitating and sometimes fatal as the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage. It can affect any part of the body, but most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. The course of this disease is unpredictable, with periods of illness (called flares) alternating with remission. Lupus erythematosus is one of the several diseases known as the great imitator because its symptoms vary so widely it often mimics or is mistaken for other illnesses, and because the symptoms come and go unpredictably. Lupus research has dramatically increased in recent years but the exact cause of the disease is unknown and there is still no consensus on whether it is a single condition or a group of related diseases. As of 2006, there is no known cure for lupus

erythematosus and treatment is restricted to dealing with the symptoms. (<URL:http://en.wikipedia.org/wiki/ Lupus_erythematosus >)

Furthermore, there is a vast range of causes for the problem and biochemical pathways that mediate the deterioration of the immune system. There is no common mechanism by which all, or even most, autoimmune diseases arise and one treatment cannot be used to treat all types of autoimmune diseases.

Hence, in the absence of a showing of correlation between all the diseases encompassed by the claims as capable of treatment by inhibiting Dipeptidyl peptidase IV activity one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of the activity dipeptidyl peptidase IV.

The amount of direction present and the presence or absence of working examples

The only direction or guidance present in the instant specification is minimal. The specification only gives a list of conditions mediated by the inhibition of Dipeptidyl peptidase IV activity. There are no working examples present for the treatment of any specific disease or disorder.

Test assays and procedure are provided in the specification at pages 118-122 for Screening of DPP-IV inhibitor and monitoring blood glucose level in the rat after administering a glucose solution followed by the claimed compound. Receptor activity is generally unpredictable and the data provided is insufficient for one of ordinary skill in

the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is an inhibitor of dipeptidyl peptidase IV activity, comprising the compound of claim 2 as an active ingredient. Furthermore, the instant claims cover "diseases" that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases would be benefited by the inhibition of dipeptidyl peptidase IV activity and would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention for an inhibitor of dipeptidyl peptidase IV activity. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the claims or amending claims to read "A pharmaceutical composition, comprising the compound of claim 2 as an active ingredient" and also deleting any duplicate claims.

V. Objections

Claim Objection-Non Elected Subject Matter

Claims 1-12 are objected to as containing non-elected subject matter. To overcome this objection, Applicant should submit an amendment deleting the non-elected subject matter.

VI. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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